EXHIBIT 4

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2007 VOL. 356 NO. 26

First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects

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ABSTRACT

BACKGROUND

The risk of birth defects after antenatal exposure to selective serotonin-reuptake inhibitors (SSRIs) remains controversial.

METHODS

We assessed associations between first-trimester maternal use of SSRIs and the risk of birth defects among 9849 infants with and 5860 infants without birth defects participating in the Slone Epidemiology Center Birth Defects Study.

RESULTS

In analyses of defects previously associated with SSRI use (involving 42 comparisons), overall use of SSRIs was not associated with significantly increased risks of craniosynostosis (115 subjects, 2 exposed to SSRIs; odds ratio, 0.8; 95% confidence interval [CI], 0.2 to 3.5), omphalocele (127 subjects, 3 exposed; odds ratio, 1.4; 95% CI, 0.4 to 4.5), or heart defects overall (3724 subjects, 100 exposed; odds ratio, 1.2; 95% CI, 0.9 to 1.6). Analyses of the associations between individual SSRIs and specific defects showed significant associations between the use of sertraline and omphalocele (odds ratio, 5.7; 95% CI, 1.6 to 20.7; 3 exposed subjects) and septal defects (odds ratio, 2.0; 95% CI, 1.2 to 4.0; 13 exposed subjects) and between the use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio, 3.3; 95% CI, 1.3 to 8.8; 6 exposed subjects). The risks were not appreciably or significantly increased for other defects or other SSRIs or non-SSRI antidepressants. Exploratory analyses involving 66 comparisons showed possible associations of paroxetine and sertraline with other specific defects.

CONCLUSIONS

Our findings do not show that there are significantly increased risks of craniosynostosis, omphalocele, or heart defects associated with SSRI use overall. They suggest that individual SSRIs may confer increased risks for some specific defects, but it should be recognized that the specific defects implicated are rare and the absolute risks are small.

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N Engl J Med 2007;356:2675-83.

Symptoms of clinical depression affect 8 to 20% of women[1,2]; during pregnancy, about 10% of women are affected,[3] and many of these women are treated with antidepressants. In the late 1980s, a new class of antidepressants, selective serotonin-reuptake inhibitors (SSRIs), appeared and rapidly gained widespread acceptance because they have fewer side effects than the older tricyclic antidepressants and pose less risk when taken in overdose.[4] However, concern has been raised about their potential effects on the fetus. Neonatal effects, known as "SSRI neonatal withdrawal syndrome" or "SSRI abstinence syndrome,"[5-9] are now well established, but the relation of antenatal SSRI exposure to birth defects remains controversial.

Early studies[9-15] demonstrated that SSRIs were not "major teratogens" similar to thalidomide or isotretinoin.[16] More recently, however, elevated risks of birth defects overall,[17,18] as well as elevated risks of omphalocele,[19] craniosynostosis,[19] and congenital heart defects,[18,20-22] have been reported in association with the use of SSRIs. One study specifically identified paroxetine as increasing the risk of omphalocele,[19] and three have associated this SSRI with congenital heart defects.[20-22] However, none of these studies considered risks of cardiac defects in relation to other specific SSRIs. Using data from the Slone Epidemiology Center Birth Defects Study, an ongoing program of case–control surveillance of medications in relation to birth defects, we evaluated these hypotheses and also considered other specific birth defects in relation to first-trimester use of specific SSRIs.

METHODS

STUDY DESIGN

The Birth Defects Study began in 1976, focusing both on testing existing hypotheses and on identifying previously unsuspected associations; the methods have been described.[23,24] Infants with any of a wide range of malformations are identified in five study centers that include the areas surrounding Boston, Philadelphia, Toronto, and San Diego, as well as a portion of New York State. Research staff identify subjects by reviewing clinical and surgical logs, reviewing admission and discharge lists, and contacting newborn nurseries and labor and delivery rooms. Subjects in New York State and, since 1998, in Massachusetts are identified from statewide birth-defect registries. Infants with isolated minor defects (e.g., accessory nipples, dislocatable hips, and low-set ears) are excluded. Nonmalformed infants were identified at study hospitals until 1998; subsequently, enrollment was expanded to include a population-based random sample of newborns in Massachusetts. This study has been approved by the institutional review boards at Boston University and other participating institutions.

Mothers of identified infants are invited to participate by completing a 45-to-60-minute interview (in person until 1998 and by telephone thereafter) within 6 months after delivery, conducted by trained study nurses who are unaware of the study hypotheses. Oral informed consent is obtained from the mothers. The interview elicits information on demographic, reproductive, and medical factors, cigarette smoking, and the consumption of alcohol and caffeine. Detailed data are collected on all medications (prescription, over-the-counter, vitamins and minerals, and herbal products) used at any time from 2 months before conception through the end of the pregnancy.

Using a multilevel approach,[25] we first ask women whether they had any of a list of specific illnesses during pregnancy and what drugs they used to treat those conditions. We then ask about use of medications for specific indications, including "anxiety," "depression," and "other psychological conditions." Finally, independent of their responses to the previous questions, each woman is asked about her use of named medications, identified by brand name, including Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), Effexor (venlafaxine), Elavil (amitriptyline), Celexa (citalopram), Luvox (fluvoxamine), Lexapro (escitalopram), and Wellbutrin (bupropion).

The current analysis was restricted to women whose last menstrual period occurred between January 1, 1993, and December 31, 2004. We excluded subjects whose infants had chromosomal defects, known mendelian inherited disorders, syndromes, defects with a known cause (e.g., fetal alcohol syndrome), and metabolic disorders (e.g., phenylketonuria and glucose-6-phosphate dehydrogenase deficiency). Among subjects, 22.7% of mothers and 25.4% of controls declined to participate. Another 15.6% of mothers and 14.7% of controls either did not respond to repeated contacts or were unavailable for interview.

ASSESSMENT OF PREVIOUSLY REPORTED ASSOCIATIONS

Previous reports have associated craniosynostosis, omphalocele, and congenital heart defects with the use of SSRIs. Because heart defects represent developmentally diverse outcomes, we created seven developmentally based subgroups.[26] In order of embryologic development, these are looping, laterality, and single-ventricle defects (e.g., situs inversus totalis and double-inlet left ventricle); conotruncal defects (e.g., tetralogy of Fallot and double-outlet right ventricle); atrioventricular canal defects (e.g., endocardial cushion defect and common atrioventricular canal defect); right ventricular outflow tract obstruction (e.g., pulmonary valve atresia or stenosis and Ebstein's anomaly); left ventricular outflow tract obstruction (e.g., aortic valve atresia or stenosis and hypoplastic left heart); septal defects (e.g., ventricular septal defect and atrial septal defect); and total or partial anomalous pulmonary venous return. A complete list is provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

A clinical geneticist trained in pediatric cardiology reviewed the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), codes of each case and, where possible, assigned the case to one or more of the seven groups. Cases were assigned to as many of these categories as their ICD codes would indicate, but in some situations, considerations of developmental processes took precedence. For example, a case with anomalous pulmonary venous return and a septal defect, along with the additional diagnosis of asplenia, was assigned to the developmentally appropriate category of "laterality defect."

EXPLORATORY ANALYSES

In addition to the defects previously associated with SSRIs, we examined other specific defects that were present in at least 100 subjects overall and at least 5 exposed subjects.

EXPOSURE

We considered first-trimester exposure to include use of any SSRI from 28 days before the last menstrual period through the fourth lunar month (112 days after the last menstrual period). The analysis of specific SSRIs excluded 79 women who took more than one SSRI during this period. To consider possible "confounding by indication," in which an apparent association between an outcome and medication is actually due to the condition for which the medication is used, we also investigated exposure to non-SSRI antidepressants (e.g., tricyclic antidepressants, bupropion, and venlafaxine; the latter has both serotonin and norepinephrine activity and represented 20% of this group). The reference group for all analyses was women not exposed to any antidepressant at any time from 56 days before the last menstrual period through the end of pregnancy. To avoid misclassification, we excluded women whose only exposure to antidepressants was between 28 and 56 days before the last menstrual period or after lunar month 4.

STATISTICAL ANALYSIS

Odds ratios and 95% confidence intervals were calculated separately for each exposure and outcome by multiple logistic regression. To assess confounding, we explored factors that were associated with exposure to any SSRI and to the risk of birth defects overall, including maternal age, maternal race or ethnic group (self-reported), maternal education, year of last menstrual period, parity, study center, first-trimester smoking, first-trimester alcohol consumption, history of a birth defect in a first-degree relative, prepregnant body-mass index, seizures, diabetes mellitus, hypertension, infertility, and first-trimester use of folic acid. Because some birth defects have been associated with obesity,[27-30] we also explored effect modification by body-mass index for each outcome with an increased risk. No statistical adjustment was made for multiple testing.

RESULTS

A total of 9849 infants with malformations and 5860 control infants were included in the analysis. Among outcomes previously reported to be associated with SSRI use, there were 127 cases of omphalocele, 115 cases of craniosynostosis, and 3724 cases of congenital heart defects; the latter included 186 looping or laterality defects, 620 conotruncal defects, 164 atrioventricular defects, 363 right ventricular outflow tract obstruction defects, 482 left ventricular outflow tract obstruction defects, 1161 septal defects, and 17 cases of anomalous pulmonary venous return.

For exploratory analyses, we identified 17 diagnosis groups that had 100 or more subjects. Six

groups were excluded from further analysis because they had fewer than 5 subjects who had been exposed to an SSRI: esophageal atresia (189 subjects, 4 exposed), absent kidney (178 subjects, 4 exposed), horseshoe or accessory kidney (127 subjects, 4 exposed), abnormal intestinal rotation (149 subjects, 3 exposed), cystic kidney (179 subjects, 2 exposed), and small intestinal atresia (129 subjects, 2 exposed).

Table 1 shows the rates of exposure to any SSRI, specific SSRIs, and non-SSRI antidepressants for each outcome and for the control subjects, who had no malformations. Because few subjects had been exposed to fluvoxamine (five subjects) and escitalopram (eight subjects), these medications were not considered further. Similarly, we did not analyze looping and laterality defects (two SSRI-exposed subjects), atrioventricular canal defects (no SSRI-exposed subjects), and anomalous pulmonary venous return (no SSRI-exposed subjects).

ASSESSMENT OF PREVIOUS HYPOTHESES

Table 2 shows the results for the 42 comparisons related to craniosynostosis, omphalocele, congenital heart defects, and the four specific cardiac-defect groups, adjusted for potential confounders.

There was no significant increase in the risk of craniosynostosis associated with the use of SSRIs overall or with individual SSRIs; only 2 of 115 subjects with craniosynostosis had been exposed to an SSRI (1 to sertraline and 1 to paroxetine). For omphalocele, 3 of 127 subjects had been exposed to an SSRI, all to sertraline (odds ratio, 5.7; 95% confidence interval [CI], 1.6 to 20.7).

We found no appreciable or significantly increased risk of congenital heart defects overall in relation to the use of SSRIs overall (odds ratio, 1.2; 95% CI, 0.9 to 1.6). However, when we assessed associations between specific heart-defect subgroups and individual SSRIs, the odds ratios ranged from 0.5 to 3.3, and two risk estimates had lower bounds that exceeded 1.0: sertraline

Table 1. Rates of Exposure to Antidepressants within Outcome Groups.

Outcome	Total No. of Subjects	Any SSRI	Fluoxetine	Sertraline	Paroxetine	Citalopram	Non-SSRI Antidepressant
				no. of subjects (%)			
Craniosynostosis	115	2 (1.7)	0	1 (0.9)	1 (0.9)	0	0
Omphalocele	127	3 (2.4)	0	3 (2.4)	0	0	1 (0.8)
Any cardiac defect	3724	100 (2.7)	31 (0.8)	32 (0.9)	25 (0.7)	5 (0.1)	23 (0.6)
Conotruncal defects	620	13 (2.1)	6 (1.0)	2 (0.3)	4 (0.6)	0	4 (0.6)
Right ventricular outflow tract obstruction defects	363	15 (4.1)	4 (1.1)	3 (0.8)	6 (1.7)	0	2 (0.6)
Left ventricular outflow tract obstruction defects	482	15 (3.1)	6 (1.2)	5 (1.0)	1 (0.2)	2 (0.4)	2 (0.4)
Septal defects	1161	32 (2.8)	10 (0.9)	13 (1.1)	6 (0.5)	2 (0.2)	10 (0.9)
Cleft lip with or without cleft palate	704	22 (3.1)	11 (1.6)	3 (0.4)	4 (0.6)	4 (0.6)	6 (0.9)
Pyloric stenosis	688	18 (2.6)	6 (0.9)	7 (1.0)	3 (0.4)	2 (0.3)	6 (0.9)
Renal-collecting-system defects	644	17 (2.6)	5 (0.8)	6 (0.9)	4 (0.6)	2 (0.3)	4 (0.6)
Hypospadias	497	14 (2.8)	3 (0.6)	3 (0.6)	3 (0.6)	4 (0.8)	5 (1.0)
Clubfoot	413	20 (4.8)	3 (0.7)	5 (1.2)	10 (2.4)	2 (0.5)	4 (1.0)
Cleft palate alone	377	7 (1.9)	3 (0.8)	0	3 (0.8)	1 (0.3)	3 (0.8)
Undescended testis	349	11 (3.2)	1 (0.3)	0	6 (1.7)	2 (0.6)	2 (0.6)
Neural-tube defects	320	5 (1.6)	0	1 (0.3)	4 (1.2)	0	1 (0.3)
Anal atresia	215	7 (3.3)	2 (0.9)	3 (1.4)	1 (0.5)	1 (0.5)	3 (1.4)
Diaphragmatic hernia	192	6 (3.1)	3 (1.6)	1 (0.5)	1 (0.5)	0	2 (1.0)
Limb-reduction defects	193	9 (4.7)	3 (1.6)	3 (1.6)	1 (0.5)	1 (0.5)	1 (0.5)
No malformations	5860	160 (2.7)	61 (1.0)	46 (0.8)	30 (0.5)	15 (0.3)	49 (0.8)

Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for Specific SSRIs in Relation to Outcomes Previously Reported to Be Associated with SSRI Use.*

Outcome	Any SSRI	Fluoxetine	Sertraline	Paroxetine	Citalopram	Non-SSRI Antidepressant
			odds ratio (95% confidence interval)			
Craniosynostosis	0.8 (0.2–3.5)	—	1.8 (0.2–14.9)	1.7 (0.2–14.4)	—	—
Omphalocele	1.4 (0.4– 4.5)	—	5.7 (1.6–20.7)	—	—	1.2 (0.2–9.3)
Any cardiac defect	1.2 (0.9–1.6)	0.9 (0.6–1.5)	1.5 (0.9–2.6)	1.4 (0.8–2.5)	0.7 (0.2–2.1)	0.8 (0.5–1.5)
Conotruncal defects	1.2 (0.6–2.1)	1.3 (0.5–3.2)	0.7 (0.2–3.3)	1.7 (0.6–5.1)	—	0.9 (0.3–2.6)
Right ventricular outflow tract obstruction defects	2.0 (1.1–3.6)	1.0 (0.2–3.4)	2.0 (0.6–6.8)	3.3 (1.3–8.8)	—	0.9 (0.2–3.8)
Left ventricular outflow tract obstruction defects	1.6 (0.9–2.9)	1.6 (0.6–4.0)	1.9 (0.6–5.8)	0.5 (0.1–3.9)	3.3 (0.7–16.0)	0.6 (0.1–2.4)
Septal defects	1.2 (0.8–1.8)	1.0 (0.5–2.2)	2.0 (1.2–4.0)	0.8 (0.3–2.2)	0.8 (0.2–4.0)	1.1 (0.6–2.4)

* Odds ratios are adjusted for maternal age; maternal race or ethnic group (self-reported); maternal education; year of last menstrual period; study center; first-trimester smoking status; first-trimester alcohol consumption; history of a birth defect in a first-degree relative; prepregnancy body-mass index; parity; presence or absence of seizures, diabetes mellitus, hypertension, or infertility; and first-trimester use of folic acid. The reference group was all women not exposed to any antidepressant. Dashes indicate no exposed subjects.

in relation to septal defects (odds ratio, 2.0; 95% CI, 1.2 to 4.0, based on 13 exposed subjects) and paroxetine in relation to right ventricular outflow tract obstruction defects (odds ratio, 3.3; 95% CI, 1.3 to 8.8, based on 6 exposed subjects). No appreciable or significantly increased risks were associated with fluoxetine (range of odds ratios, 1.0 to 1.6), nor were there appreciable or significant associations between non-SSRI antidepressants and any of the specific birth defects examined.

EXPLORATORY ANALYSES

Table 3 presents risk estimates for other birth defects, adjusted for potential confounders. Among 66 comparisons, 4 had lower confidence bounds that exceeded 1.0: sertraline in relation to anal atresia and limb-reduction defects (3 exposed subjects for each defect) and paroxetine in relation to neural-tube defects and clubfoot (4 and 10 exposed subjects, respectively). One association, that between paroxetine use and undescended testis, had a lower confidence bound of 1.0. For non-SSRI antidepressants, risk estimates ranged from 0.6 to 1.2, with one exception: an odds ratio of 2.2 for anal atresia, based on three exposed subjects (lower 95% confidence bound, 0.6). For positive associations, no mothers of exposed subjects reported exposure to any suspected teratogenic drugs.[17]

We also investigated effect modification by body-mass index for associations with elevated risks. Although there was a tendency for risks to be higher in overweight and obese women than in women of normal weight, there were too few exposed women in each category to generate stable results (data not shown).

DISCUSSION

Our analysis did not confirm previously reported associations between overall use of SSRIs and craniosynostosis, omphalocele, or heart defects as a group. Alwan et al.[19] previously reported increased risks of craniosynostosis and omphalocele associated with maternal SSRI use and found paroxetine to be most strongly associated with omphalocele. We did not replicate these findings: no infant with omphalocele and only one with craniosynostosis was exposed to paroxetine among our study population. The only significant association we found between either of these two defects and the use of SSRIs was an association between sertraline use and omphalocele (odds ratio, 5.7; 95% CI, 1.6 to 20.7), which was based on only three exposed subjects.

We did not find significantly increased risks of congenital heart defects overall associated with overall use of SSRIs or of non-SSRI antidepressants. However, using an embryologically based

Table 3. Adjusted Odds Ratios and 95% Confidence Intervals for Specific SSRIs in Relation to Outcomes Not Previously Reported to Be Associated wtih SSRI Use.*

Outcome	Any SSRI	Fluoxetine	Sertraline	Paroxetine	Citalopram	Non-SSRI Antidepressant
			odds ratio (95% confidence interval)			
Cleft lip with or without cleft palate	1.5 (0.9–2.5)	1.8 (0.8–3.8)	1.1 (0.3–3.8)	1.2 (0.4–3.6)	3.2 (0.9–11.9)	1.2 (0.2–9.3)
Pyloric stenosis	1.1 (0.6–1.8)	0.9 (0.4–2.1)	1.7 (0.7–4.1)	0.7 (0.2–2.6)	2.1 (0.4–10.4)	1.1 (0.5–3.1)
Renal-collecting-system defects	1.1 (0.7–1.9)	1.0 (0.5–2.3)	1.7 (0.7–4.2)	1.0 (0.3–3.3)	1.9 (0.4–8.8)	0.7 (0.2–3.2)
Hypospadias	1.2 (0.6–2.2)	0.7 (0.2–2.4)	1.2 (0.4–4.2)	1.0 (0.3–3.3)	1.9 (0.4–8.8)	0.7 (0.3–2.4)
Clubfoot	2.2 (1.4–3.6)	0.8 (0.2–2.5)	2.4 (0.9–6.2)	5.8 (2.6–12.8)	2.7 (0.5–13.1)	1.0 (0.3–3.2)
Cleft palate alone	0.9 (0.4–2.0)	1.0 (0.3–3.5)	—	1.5 (0.4–5.3)	2.3 (0.4–12.6)	0.9 (0.3–3.2)
Undescended testis	1.3 (0.7–2.5)	0.4 (0.1–2.6)	—	2.8 (1.0–7.8)	3.1 (0.6–15.5)	0.7 (0.2–3.0)
Neural-tube defects	0.6 (0.2–1.4)	—	0.8 (0.1–6.3)	3.3 (1.1–10.4)	—	0.6 (0.1–2.4)
Anal atresia	1.9 (0.8–4.3)	1.4 (0.3–6.1)	4.4 (1.2–16.4)	1.0 (0.1–7.8)	3.0 (0.3–28.2)	2.2 (0.6–7.8)
Diaphragmatic hernia	1.8 (0.7–4.2)	2.0 (0.6–6.9)	1.5 (0.2–11.5)	1.2 (0.2–8.9)	—	1.1 (0.3–5.1)
Limb-reduction defects	1.7 (0.9–3.4)	1.7 (0.5–5.7)	3.9 (1.1–13.5)	1.0 (0.1–8.3)	4.0 (0.5–33.9)	0.7 (0.7–5.2)

* Odds ratios are adjusted for maternal age; maternal race or ethnic group (self-reported); maternal education; year of last menstrual period; study center; first-trimester smoking status; first-trimester alcohol consumption; history of a birth defect in a first-degree relative; prepregnancy body-mass index; parity; presence or absence of seizures, diabetes mellitus, hypertension, or infertility; and first-trimester use of folic acid. The reference group was all women not exposed to any antidepressant. Dashes indicate no exposed subjects.

classification of heart defects, we found a doubling of the risk of septal defects associated with sertraline use (odds ratio, 2.0), based on 13 exposed subjects, and a tripling of the risk of right ventricular outflow tract obstruction defects associated with paroxetine use (odds ratio, 3.3), based on 6 exposed subjects. The latter finding is supported by an odds ratio of 2.5, based on seven exposed subjects (95% CI, 1.0 to 9.6), identified by Alwan et al. in an article in this issue of the *Journal*.[31] These more detailed findings were derived from two case–control surveillance studies with data sets large enough to consider both specific malformations and specific SSRIs.

Our observations of significant increases in the risk of selected cardiac defects with the use of certain SSRIs may reflect different teratologic effects among specific drugs within a given pharmacologic class.[32] For SSRIs, this possibility is supported by the fact that various class members have parent compounds and metabolites with different pharmacologic characteristics.[33-35] However, we cannot rule out the possibility of chance associations, given the multiple comparisons performed.

The previously unreported associations we identified warrant particularly cautious interpretation. In the absence of preexisting hypotheses and the presence of multiple comparisons, distinguishing random variation from true elevations in risk is difficult. Despite the large size of our study overall, we had limited numbers to evaluate associations between rare outcomes and rare exposures. We included results based on small numbers of exposed subjects in order to allow other researchers to compare their observations with ours, but we caution that these estimates should not be interpreted as strong evidence of increased risks. On the basis of the magnitude of the risk estimate and the number of exposed subjects, certain associations warrant further exploration: sertraline in relation to anal atresia and limb-reduction defects, and paroxetine in relation to neural-tube defects and clubfoot.

Among all defects evaluated, we found that, for fluoxetine, no risk estimate exceeded 2.0 and none had a lower confidence bound exceeding 1.0. For non-SSRI antidepressants, no risk estimate exceeded 1.2, except for anal atresia, and the confidence interval for that estimate, based on three exposed subjects, did not exclude 1.0. On the other hand, sertraline and paroxetine were

associated with significant increases in specific birth defects, none of which were common to both drugs.

Recall bias may be a concern, since mothers of infants with malformations may recall and report exposures more completely than mothers of the control subjects who had no malformations. However, we consider this unlikely, since antidepressants are typically used on a regular basis for nontrivial indications, and recall of their use may be less subject to such bias than medications used infrequently and more casually. Further, the use of a multilevel structured questionnaire to identify medication use should minimize recall bias[25] and has been shown to elicit rates of use similar to estimates from marketing data.[36] Moreover, the null effects we observed among the non-SSRI antidepressants argue against recall bias, and recall bias would not explain risks associated with some individual SSRIs but not with others. Selection bias is unlikely, since mothers are invited to participate without knowledge of exposure. Detection bias is also unlikely, given the differential effects of non-SSRIs as compared with specific SSRIs and variability in the effects among specific SSRIs.

Confounding by uncontrolled factors is always possible in observational studies. We considered a large number of relevant demographic, medical, and reproductive factors. A major potential confounder is the effect of depression itself, unrelated to drug treatment. However, the absence of significantly increased risks of various birth defects associated with the use of non-SSRI antidepressants suggests that depression itself is unlikely to be the cause of the defects studied. The possibility that chance accounts for some or all of these results cannot be ruled out, especially in view of the many comparisons that were made in these analyses (42 in assessing previously reported associations and 66 in exploratory analyses). For that reason, we place greater reliance on findings that are consistent with previous studies, and we await further research on newly reported associations.

Our understanding of the risks to the fetus of SSRI use has evolved from initial small cohort studies that ruled out major teratogenic risks to more recent efforts that have raised questions about moderate overall increases in risk as well as increases in broad categories of defects, such as cardiac anomalies. The current study suggests that specific SSRIs may increase the risk of specific birth defects, and further studies will need sufficient power to pursue these important clinical questions. In the meantime, it is important to keep in perspective that the absolute risks of these rare defects are small. For example, the baseline prevalences of anal atresia[37] and right ventricular outflow tract obstruction defects[26] are each estimated to be about 5.5 cases per 10,000 live births; thus, even if a specific SSRI increased rates by a factor of four, the risk of having an affected child would still be only 0.2%.

The Slone Epidemiology Center Birth Defects Study was supported in part by grants from the National Institute of Child Health and Human Development (HD27697) and the National Heart, Lung, and Blood Institute (HL50763). Additional support was provided by Aventis and Sanofi Pasteur. This data analysis was supported in part by a contract from GlaxoSmithKline, the manufacturer of Paxil (paroxetine). Responsibility for this analysis and the manuscript rests solely with the authors.

Drs. Louik, Mitchell, and Werler report receiving support from Sanofi Pasteur to identify rates of use of various vaccines in pregnancy. Dr. Mitchell reports participating (unpaid) in an advisory committee for GlaxoSmithKline's Lamotrigine Pregnancy Registry and serving as principal investigator of the Isotretinoin Survey (2002–2006), sponsored by Barr Pharmaceuticals, Ranbaxy Laboratories, and Genpharm; all these companies manufacture generic forms of antidepressants included in this study. Dr. Werler reports participating in scientific advisory boards for pregnancy registries of rheumatoid arthritis medications marketed by Sanofi-Aventis, Abbott Laboratories, and Amgen. No other potential conflict of interest relevant to this article was reported.

We thank Dawn Jacobs, Fiona Rice, Rita Krolak, Kathleen Sheehan, Karen Bennett Mark, Clare Coughlin, Nastia Dynkin, Nancy Rodriquez-Sheridan, and Meghan Malone-Moses for their assistance in data collection and computer programming; the staff of the Massachusetts Department of Public Health Center for Birth Defects Research and Prevention, Charlotte Druschel and the New York State Health Department, and Christina Chambers and Kenneth Jones of the University of California, San Diego (UCSD), as well as the medical and nursing staff at the following participating hospitals for assistance with case ascertainment: Baystate Medical Center, Beth Israel Deaconess Medical Center, Boston Medical Center, Brigham and Women's Hospital, Brockton Hospital, Cambridge Hospital, Caritas Good Samaritan Medical Center, Charlton Memorial Hospital, Boston Children's Hospital, Emerson Hospital, Falmouth Hospital, Haverhill–Hale Hospital, Jordan Hospital, Kent Hospital, Lawrence General Hospital, Lowell General Hospital, Melrose–Wakefield Hospital, Metro West Medical Center–Framingham, Mt. Auburn Hospital, New England Medical Center, Newton–Wellesley Hospital, North Shore Medical Center, Rhode Island Hospital, Saints Memorial Medical Center, South Shore Hospital, Southern New Hampshire Medical Center, St. Elizabeth's Medical Center, St. Luke's Hospital, St. Vincent Hospital, University of Massachusetts Memorial Health Care, Women & Infants' Hospital, Abington Memorial Hospital, Albert Einstein Medical Center, Alfred I. duPont Hospital for Children, Bryn Mawr Hospital, Chester County Hospital, Children's Hospital of Philadelphia, Christiana Care Health Services, Community Hospital, Crozer–Chester Medical Center, Doylestown Hospital, Frankford Hospital, Hahnemann University

Hospital, the Hospital of the University of Pennsylvania, Lankenau Hospital, Lancaster General Hospital, Lehigh Valley Hospital, Nanticoke Memorial Hospital, Pennsylvania Hospital, Sacred Heart Hospital, St. Christopher's Hospital for Children, St. Mary Medical Center, Temple University Health Sciences Center, Reading Hospital & Medical Center, Thomas Jefferson University Hospital, Grand River Hospital, Guelph General Hospital, Hamilton Health Sciences Corporation, the Hospital for Sick Children, Humber River Regional Hospital–Church Site, Humber River Regional Hospital–Finch Site, Joseph Brant Memorial Hospital, Lakeridge Health Corporation, London Health Sciences Center, Mt. Sinai Hospital, North York General Hospital, Oakville Trafalgar Memorial Hospital, Scarborough Hospital–General Division, Scarborough Hospital–Grace Division, St. Joseph's Health Centre–London, St. Joseph's Health Centre–Toronto, St. Joseph's Healthcare–Hamilton, St. Michael's Hospital, Sunnybrook & Women's College Health Sciences Center, Toronto East General Hospital, Toronto General Hospital, Trillium Health Center, William Osler Heath Centre, York Central Hospital, York County Hospital, Alvarado Hospital, Balboa Naval Medical Center, Camp Pendleton Naval Hospital, Children's Hospital and Health Center, Kaiser Zion Medical Center, Palomar Medical Center, Pomerado Hospital, Scripps Mercy Hospital, Scripps Memorial Hospital–Chula Vista, Scripps Memorial Hospital–Encinitas, Scripps Memorial Hospital–La Jolla, Sharp Chula Vista Hospital, Sharp Coronado Hospital, Sharp Grossmont Hospital, Sharp Mary Birch Hospital, Tri-City Medical Center, and UCSD Medical Center. We also thank all the mothers who participated in the study.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007;356:2675-83.

Web-Only Supplement: Heart Defect Codes

I. Situs Anomalies and Looping Defects

Situs inversus totalis, heterotaxy
Asplenia
Accessory spleen
Corrected transposition of the great arteries/L-transposition of the great arteries (TGA)
Ventricular inversion
Common or single ventricle
Double inlet left ventricle
Double inlet right ventricle

II. Conotruncal and Major Arch Anomalies

Truncus arteriosus/persistent truncus
d-Transposition great arteries (d-TGA)
Transposition great vessels nos
Transposition great arteries, complete
Taussig-Bing Syndrome/double outlet right ventricle
Tetralogy of Fallot
Tetralogy of Fallot with atrial septal defect
Pseudotruncus (tetralogy of Fallot with pulmonary atresia)
Conoventricular ventricular septal defect
Vascular ring
Double aortic arch
Interrupted aortic arch

III. Septal Defects

VSD—supracristal, subarterial, type I
VSD—perimembranous, type II
VSD—muscular, type IV
Multiple VSDs
VSD nos
Atrial septal defect (ASD), secundum type
Auricular septal defect nos
ASD, other specified
ASD nos

IV. AV Canal, AV Septal Defects

Common atrioventricular (AV) canal
Atrioventricular septal defect
Complete AV septal defect
Common atrioventricular (AV) canal-type VSD
VSD inflow, canal-type, type III
Incomplete AV canal
ASD primum type
Common atrium
Other endocardial cushion defect
Endocardial cushion defect nos

V. Right Ventricular Outflow Tract Obstruction

Pulmonary valve absent or atresia
Pulmonary valve stenosis or narrowing
Other pulmonary valve anomalies
Tricuspid valve stenosis or narrowing
Tricuspid valve atresia or narrowing
Tricuspid valve atresia or stenosis nos
Other tricuspid valve anomalies/hypoplasia tricuspid valve
Ebstein anomaly
Pulmonary infundibular (subvavular) stenosis
Pulmonary artery stenosis or narrowing
Pulmonary artery atresia or absence
Pulmonary artery atresia or stenosis, nos
Pulmonay artery stenosis /with VSD
Pulmonary artery atresia /with VSD, not Tetralogy type
Pulmonary artery atresia/stenosis nos / with VSD

VI. Left Ventricular Outflow Tract Obstruction

Aortic valve stenosis or narrowing
Aortic valve atresia or absent
Aortic valve atresia/stenosis nos
Subaortic stenosis
Other aortic valve anomalies/ hypoplasia aortic valve
Mitral valve stenosis or narrowing
Mitral valve atresia or absence
Mitral valve atresia/stenosis nos
Other mitral valve anomalies
Hypoplastic left heart syndrome
Cor triatriatum
Shone's complex
Preductal coarctation aorta
Postductal coarctation aorta
Juxtaductal coarctation aorta
Coarctation aorta with VSD
Coarctation aorta nos
Other coarctation aorta
Aorta stenosis or narrowing
Aorta atresia, stenosis nos
Aorta hypoplasia, tubular hypoplasia aorta
Supra-aortic stenosis

VII. Anomalous Pulmonary Venous Return

Total anomalous pulmonary venous return
Partial anomalous pulmonary venous return